DETAILED ACTION

Response to Amendment

Claims 45 and 46 have been amended as requested in the amendment filed on 21 February 2008. Following the amendment, claims 25-29, 43 and 45-47 are pending in the instant application.

Claims 25-29 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicants timely traversed the restriction (election) requirement in Paper filed on 13 March 2000.

Claims 43 and 45-47 are under examination in the instant office action.

This application contains claims 25-29 drawn to an invention nonelected with traverse in Paper filed on 13 March 2000. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The rejection of claims 43 and 45 under 35 U.S.C. 103(a) as being unpatentable over Varon et al. in view of Kamata et al. is maintained for reasons of record and as set forth below.

In the reply filed on 21 February 2008, Applicants argue that there is no evidence in Kamata et al. that a C3 ADP-ribossyl transferase ("CART") would promote neurite outgrowth in a CNS environment. Applicants assert that the dorsal root ganglia (DRG) treated in Kamata et al. are in the peripheral nervous system (PNS) and not the central nervous system (CNS) and that it is well established that the microenvironment and

cellular makeup of the CNS are very different from those of the PNS, and that factors within the CNS microenvironment, including CNS myelin, act to inhibit nerve regeneration. Applicants thus allege that the skilled artisan would have no expectation of success in using a CART to increase neurite regeneration in the CNS based on Kamata et al.'s disclosure of a PNS model. Applicants assert that the Kamata et al. disclosure is directed to *in vitro* assays and that *in vitro* results are not necessarily indicative of *in vivo* effects. Applicants allege that the crux of the disclosure of Kamata et al. is that CART demonstrated neurite-inducing activity in a PNS culture system (i.e., DRG cultures) and not that CART is a neurotrophic factor. Applicants assert that Kamata et al. does not state or suggest that CART belongs to a family of neurotrophic factors. Applicants assert that all neurotrophic factors are not interchangeable such that CART could not be exchanged with any of a number of neurotrophic factors, such as NGF. Applicants state that a CART is an exogenous enzyme derived from bacteria that does not bind to specific receptors but that "specifically ADP-ribosylate and inhibit the action of the rho family of GTP-binding proteins." Applicants assert that this is in contrast to NGF, which is an endogenous polypeptide that is produced by the target of innervating neurons and that acts on receptors located on the cell surface of neurons. Applicants conclude that since the members of the family of neurotrophic factors are structurally and functionally distinct from a CART, one of ordinary skill in the art would not consider CARTs and neurotrophic factors, such as NGF, to be interchangeable. Applicants acknowledge that the abstract of Kamata et al. states that CART "evoked the outgrowth of neurites from chick ganglion as effectively as nerve growth factor."

However, Applicants assert that CART was far less efficient than NGF at evoking the outgrowth and that Kamata et al. reports that it took a large increase in the amount of CART relative to NGF to induce neurite outgrowth of cultured chick embryonic ganglia. Thus, Applicants conclude that one of ordinary skill in the art would not have considered that CART and NGF would be interchangeable in an *in vitro* PNS system, much less interchangeable for administration to the CNS of a patient. Applicants also allege that Kamata et al. teaches away from the claimed methods because Kamata et al. states that CART induces "dysfunctional" changes in the cytoskeleton of cultured cells. Finally, Applicants remind the Examiner of the unexpected results described in Example II of the instant application and referred to on page 9, second last paragraph, of the Response submitted May 24, 2007.

Applicants' arguments have been fully considered and are not found persuasive. Although CART and neurotrophic factors such as NGF may exert their trophic effects on neurons through different mechanisms, all of these agents still have neurotrophic activity as evidenced by the prior art. Thus, the skilled artisan would not be dissuaded from using CART in neurotrophic methods simply because it does not work through the same mechanism as other neurotrophic agents or simply because it does not belong to the “neurotrophic factor family” of proteins. Furthermore, it is well established in the art that methods are used to test neurotrophic activities of potential compounds *in vitro* before using these compounds *in vivo*. Regardless, a role for the involvement of rho-related small G-proteins in the regulation of neurite outgrowth *in vivo* had already been implicated at the time of filing (see Jin et al. J.Neurosci (1997), p.6256: citation AL on

IDS dated 12 July 1999 and Zipkin et al. Cell (1997): citation CS on IDS dated 12 July 1999). Thus, any different effect which may or may not be demonstrated by using CART *in vivo* would not have dissuaded the artisan from trying to use CART *in vivo*; the artisan would still at least be motivated to try to use CART *in vivo*. Regarding Applicants' assertion that the skilled artisan would not have considered that CART and NGF would be interchangeable *in vitro* or *in vivo* because more CART was necessary to evoke the same response evoked by NGF, the authors of the Kamata et al. reference concluded that CART and NGF would be interchangeable as neurotrophic agents since as pointed out by Applicants, the abstract states that CART "evoked the outgrowth of neurites from chick ganglion as effectively as nerve growth factor." Given the authors' explicit conclusion from their data, the skilled artisan would not need to make any intellectual leap in considering that CART has neurotrophic activity and could be used in methods where NGF is indicated.

Regarding Applicants' assertion that the Kamta et al .reference teaches away from the claimed invention, the statement referred to by Applicants concerns GOTO cells and not the DRG cells referred to in the abstract. Thus, Applicants' assertion is irrelevant to the neurotrophic effects of CART disclosed in DRG cells. Applicants' assertion that the invention is predicated on an unexpected result, typically involves synergism, an unpredictable phenomenon highly dependent upon specific proportions and/or amounts of particular ingredients used in particular methods. Any mixture of the components embraced by the claims which does not exhibit an unexpected result (e.g. synergism) is therefore ipsto facto unpatentable. Given that the instant claims are

directed to increasing CNS neurite regeneration *in vivo* in a patient with a traumatic spinal cord lesion with "a C3 ADP-ribosyl transferase," i.e. any C3 ADP-ribosyl transferase, and given that the results disclosed in Example 2 of the instant specification are directed to treatment of retinal neurons *in vitro* and treatment of optic nerve fibers *in vivo*, both with a particular C3 ADP-ribosyl transferase, the claims are not commensurate in scope with the alleged unexpected results. Therefore, the rejection of claims 43 and 45 under 35 U.S.C. 103(a) is maintained.

The rejection of claims 46 and 47 under 35 U.S.C. 103(a) as being unpatentable over Varon et al. in view of Kamata et al., further in view of U.S. Patent No. 5,134,121 to Mobley et al. is maintained for reasons of record and as set forth below.

In the reply filed on 21 February 2008, Applicants argue that none of the references discloses CART fragments at all. Applicants disagree that because the '121 patent teaches peptide fragments of NGF in the treatment of neurological diseases, it would have been obvious in view of all three references to use fragments of CART for this purpose. Applicants allege that as pointed out above, the skilled artisan would not have considered using a full-length CART for the treatment of CNS injuries. Applicants further allege that the artisan would have been even less likely to have considered using CART fragments, particularly Rho family inhibitory fragments, for this purpose. Applicants assert that while the '121 patent does disclose NGF peptides that could be useful in treatment of neurological diseases, it provides no hint of using a CART or CART fragments for this purpose. Applicants assert that given the structural and

functional differences between NGF and CARTs discussed above, a teaching that NGF fragments could be used to treat neurological diseases says nothing about the use of CART fragments.

Applicants' arguments have been fully considered and are not found persuasive. As set forth above, contrary to Applicants' assertion, the skilled artisan *would* have considered using a full-length CART for the treatment of CNS injuries. Regarding Applicants assertion that while the '121 patent does disclose NGF peptides that could be useful in treatment of neurological diseases, it provides no hint of using a CART, let alone CART fragments for this purpose, Applicants are reminded that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). As stated previously, the Varon et al. reference teaches various model systems utilizing *in vivo* administration of neurotrophic agents (e.g. NGF) to promote neuronal outgrowth in the CNS in a spinal cord injury model. Upon reading the disclosure of the Varon et al. reference, the skilled artisan would have recognized the desirability of developing improved methods of treating traumatic spinal cord injury. Furthermore, the Kamata et al. reference teaches chick dorsal root ganglia (DRG) induced nerve outgrowth via administration of CART that is at least as effective as DRG outgrowth induced via NGF. Moreover, the '121 patent teaches NGF and NGF fragments that are useful in the treatment of multiple neurological diseases through promotion of neurite outgrowth (cols. 2, 3, 6-7 and 16-18). The patent further teaches that a suitable assay to screen

for such molecules is via assessing the ability of a molecule to promote neuronal outgrowth in cultured dorsal root ganglia cultures (see Bioassay with dorsal root ganglia neurons, cols. 19-20).

As evidenced by the prior art, the skilled artisan would have known that CART is a neurotrophic agent that is at least as effective as NGF and that neurotrophic agents and their fragments are useful in providing neurite outgrowth in spinal cord injury. Thus, it would have been obvious to the person of ordinary skill to try methods of increasing neurite regeneration in the CNS via administration of CART functional fragments to a patient after spinal cord injury in an attempt to provide an improved method of treating SCI. As evidenced by the '121 patent, the artisan is armed with a suitable assay for determining which fragments of CART would be useful in such neurostimulatory treatment methods. Applicants are reminded that only a reason, suggestion or motivation need appear in the cited prior art in order to combine references under 35 U.S.C. 103. Pro Mold Tool Col. v. Great Lakes Plastics, Inc., 75 F.3d 1568, 1573, 37 USPQ2d 1626, 1629 (Fed. Cir. 1996). Therefore, as set forth above, the rejection of claims 46 and 47 under 35 U.S.C. 103(a) is maintained.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicants are reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregory S. Emch whose telephone number is (571) 272-8149. The examiner can normally be reached 9:00 am - 5:30 pm EST (M-F).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey J. Stucker can be reached at (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Gregory S. Emch/

Gregory S. Emch, Ph.D.
Patent Examiner
Art Unit 1649
04 June 2008

/Elizabeth C. Kemmerer/
Primary Examiner, Art Unit 1646